REMARKS

The specification has been amended to add section heading where appropriate. The specification has been amended to delete the reaction scheme on page 29 and a formal drawing is being submitted to include the substance of the deleted reaction scheme.

A new Abstract in compliance with 37 CFR1.121(b) is being submitted on a separate sheet of paper.

Claims 1-3 and 5-15 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which is not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Reconsideration is requested.

Claim 1 has been amended to insert the deleted language . For this reason, it is requested that this ground of rejection be withdrawn.

Claims 8-9 and 14 have been rejected under 35 U.S.C.112, first paragraph as not being enabling.

Reconsideration is requested.

The Examiner has stated that there is no evidence that the claimed compounds are effective to treat various diseases. The present application includes information regarding data that the applicants have obtained from receptor binding assays. The biological efficacy of compounds believed to be effective as tachykinin receptor antagonists may be confirmed by an assay which measures binding to NK-1 and NK-2 receptor sites as described on page 27 of the present specification.

. The antagonist activity at the NK-2 receptor of compounds of the present invention has been determined on the rabbit isolated pulmonary artery and the hamster isolated trachea preparations, two bioassays endowed with two putative NK-2 receptor subtypes.

Furthermore, it is well known that the diseases indicated in the specification are linked with the activity of NK-2 receptors, therefore compounds which have an antagonistic activity on these receptors (activity which is demonstrated *in vitro*) are useful in the treatment of such diseases.

Applicants thank the Examiner for his suggestions on amending the claims that are incorporated herein. The preferred arrangements of the specification have been adopted. In Claim 1, line 1, the term "general" has been eliminated. In Claim 2, line 1 the term "compounds" has been rewritten in the singular. Also in Claim 2, third line from last, the left-handed bracket has been removed. Further, as suggested by the Examiner, in Claim 3 the term TFA has been defined, as trifluoro-acetic acid, and referenced throughout. The superfluous periods in Claim 3 have also been removed. In Claim 5 the term "excipients", and in Claim 6 and 7, the term "antagonists" have all been placed in the singular.

The term "anxiolytics" in Claim 9 has been rewritten in the singular. In Claims 7 and 11-13 the abbreviation "NK-2" has been explained as neurokinin-2.

Claim 10 has been rewritten to recite a method of antagonizing "tachykinin receptors," not tachykinin itself. Also in Claim 10 the term "tachykinin peptide receptors" has been shortened to "tachykinin receptors".

At page 7 of the Office Action

Claims1-2 were rejected under 35 U.S.C. §102(b) as being anticipated by Rothe, M. (*Pept Proc Eur Pept Symp* 14th, 71-8, 1976). Specifically, the Examiner stated that Claim 1 includes the compound cyclo-Val-Val-Phe-Phe. This limitation has been introduced into Claim 1. In addition, the recitation: "when R_1 and R_2 are benzyl or 4-hydroxybenzyl, R_3 and R_4 are not isopropyl ." As stated by the Examiner, this limitation eliminates the 35 U.S.C. §102(b) rejection based on Kitakabake, (*Peptide Chemistry*, 17, 7, 1980). The Examiner also noted that the 35 U.S.C. §103 rejection for obviousness would not be overcome by this amendment.

Applicant respectfully transverses the rejection and requests reconsideration thereof.

The presence of the same four amino acids in the compound found in Kitakabake do not render the compounds structurally similar enough to create a 35 U.S.C. §103 rejection for obviousness. The ordering of the amino acids within the

present invention leads to vastly different interactions then would the ordering within the disclosed prior art. Had the totality of the present invention been such that movement of amino groups within its structure had no effect on the chemical properties of the compound, we would see a perfectly symmetrical structure. This is not the case at hand. The R_1 and R_2 groups are in very different chemical locations to that of the R_3 and R_4 groups. A change in their presence would create a change in the compound's overall affect on the NK-2 receptors, as well as a myriad of other interactions within the human body.

Furthermore the existence of Valine as the R1 and R2 is not within the present Markush group of the existing claims. Therefore while Kitakabake, may contain the same amino acids, they are not in the same configuration, nor are they even allowable according to the parameters of the present invention.

The present invention is distinctly different from Kitakabake, which does not teach or address main features of the Applicant's invention. Notwithstanding, no teaching is provided that would motivate anyone to modify Kitakabake.

The present invention represents a significant advantage over the prior art and avoids disadvantages of the prior art compositions. The prior art is limited to the disclosure of cyclic hexapeptides, bicyclic hexapeptides and cyclic hexapseudopeptides with NK-2 activity. However, there remains a need for more potent and selective NK-2 receptor antagonists. The pA_2 of between 5 and 9 indicates that the compounds of the present invention are potent and selective NK-2 receptor antagonists. The claimed compounds are structurally diverse from the prior art in that they have a lower molecular weight and are monocyclic with only four bifunctional residues linked together via peptide or pseudopeptide bonds. Such activity could not be predicted from the prior art that contains no relevant teachings as to predicted activity.

There is no teaching or direction to modify the prior art in such a manner that the claimed compounds would be discovered. Accordingly, it is urged that the unique structural and functional composition of the present application is unobvious. Given the aforementioned distinctions, it is maintained that the Kitakabake reference does not teach or suggest the present invention. For these reasons, it is requested that the rejections to the present claims be withdrawn.

Based on the amendments, applicant respectfully submits that all of Claims 1-15 are now allowable over the prior art and that the present application is in proper form for allowance.

Favorable consideration and early allowance is respectfully requested and earnestly solicited.

Respectfully submitted,

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Version with Markings to Show Changes Made:

IN THE SPECIFICATION

Kindly amend the specification as follows:

Page 1, line 3, rewrite heading "Scope of the Invention" as:

--Background of the Invention--

Page 3, line 9, rewrite heading "State of the Art" as:

--Description of the Related Art--

Page 4, line 5, insert:

--Brief Description of the Drawing--

--FIG.1 is a reaction scheme for the general synthesis of compounds of formula (1).--

Delete the paragraph that begins at page 6, line 13 and insert the following:

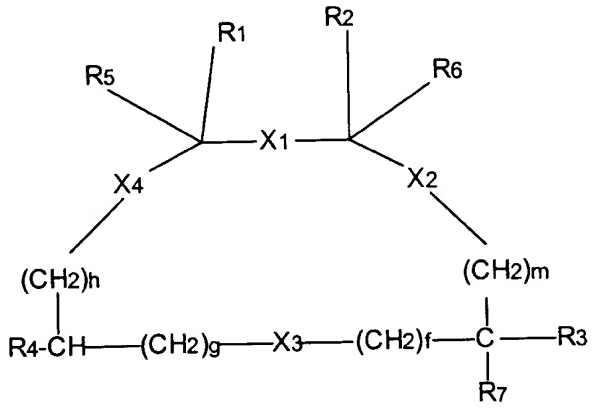
--To provide an example, [the attached diagram] Fig.1 presents the general synthesis of compounds of formula (I) in which $X_1 = X_2 = X_3 = X_4 =$ -CONH--.

Delete page 29.

IN THE CLAIMS:

Kindly amend Claims 1-13 as follows:

1. (Amended) A monocyclic compound having the [general] formula (l):



in which:

X_1, X_2, X_3, X_4, which may be the same or different from one another, is selected from the group consisting of -CONR-, -NRCO-, -OCO-, -COO-, $-CH_2NR-$ and $-NR-CH_2-$, where R is H or a C_{1-3} alkyl or benzyl;

f,g, h, m, which may be the same or different form one another, represent a number selected from the group consisting of 0, 1 and 2;

R_1 and R_2, which may be the same or different from one another, represent a $-(CH_2)_r-$ Ar group, where r = 0, 1, 2 and where Ar is an aromatic group selected from the group consisting of: benzene, naphthalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, and benzo-imidazole, said Ar group being possibly substituted with a maximum of two residues selected from the group consisting of C_{1-3} alkyl or halo-alkyl, C_{1-3} alkoxyl, C_{2-4} amino-alkoxyl, halogen, OH, NH_2, and $NR_{13}R_{14}$ where R_{13} and R_{14}, which may be the same or different from one another, represent hydrogen or C_{1-3} alkyl;

wherein R_3 is selected from the group consisting of:

-hydrogen,

-linear or branched alkyl having the formula C_nH_{2n+1}, with n= 1-5, cyclo-alkyl or alkylcyclo-alkyl groups having the formula C_nH_{2n+1}, with n= 5-9,

$-(CH_2)_r$-Ar_1 group, where r= 0, 1, 2 and where Ar_1 is an aromatic group selected from the group consisting of: benzene, naphthalene, thiophene, benzothiophene, pyridine, quinoline, indole, furan, benzofuran, thiazole, benzothiazole, imidazole, and benzo-imidazole, said Ar_1 group being possibly substituted with a maximum of two residues selected from the group consisting of C_{1-3} alkyl or halo-alkyl, C_{1-3} alkoxyl or amino-alkoxyl, halogen, OH, NH_2 and $NR_{13}R_{14}$ where R_{13} and R_{14}, which may be the same or different from one another, represent hydrogen or C_{1-3} alkyl;

wherein R_4 is selected from the group consisting of:

-hydrogen or C_{1-6} alkyl,

- L-Q, where L is a chemical bond or a linear or branched C_{1-6} alkyl residue and Q is selected from the group consisting of:

i) H, OH, OR_9, NH_2, NR_9R_{10}, guanidine, sulfate, phosphonate and phosphate where R_9 and R_{10}, which may be the same or different from one another, represent a hydrogen C_{1-3} alkyl group, C_{1-3} hydroxyalkyl, C_{1-3} dihydroxyalkyl, C_{1-3}alkyl-$CONHR_{12}$, C_{1-3}alkyltetrazole, C_{1-3}alkyl-COOH or wherein R_9R_{10} joined together form with the N-atom a saturated 4-6 membered heterocycle possibly containing a further heteroatom selected from the group consisting of N, O and S and wherein R_{12} is a mono-, di-, tri-glycosidic group possibly protected with one or more C_{1-3}-acyl groups or substituted with amino-groups or C_{1-3} acylamino-groups;

ii) COOH, tetrazole, SO_2NH_2, $SO_2NHCOOR_8$, $CONHR_8$, $NHCOR_8$, where R_8 represents a linear or cyclic C_{1-6} alkyl chain containing one or more polar groups selected from the group consisting of: OH, $NR_{15}R_{16}$, COOH, $CONHR_{12}$, PO_3H and SO_3H, OR_{11} and where R_{15} and R_{16}, which may be the same or different from one another, represent a hydrogen or C_{1-3} alkyl group, and where R_{11} is a C_{1-3} alkyl or C_{2-4} amino-alkyl chain, R_{12} is a mono-, di-, tri-glycosidic group possibly protected with one or more C_{1-3}acyl groups or substituted with amino-groups or C_{1-3}acylamino-groups or $R_{15}R_{16}$ joined together form with the N-atom a saturated 4-6 membered heterocycle possibly substituted with C_{1-3}alkyl-groups or with saturated 4-6 membered heterocycle-groups containing at least an N-atom;

iii) $COOR_{17}$, $CONHR_{12}$, OR_{12} where R_{12} is a mono-, di-, tri-glycoside group

possibly protected with one or more C_{1-3} acyl groups or substituted with amine or C_{1-3} acylamine groups and R_{17} is a group R_{12} as above defined or a group C_{1-3} alkyl, C_{1-3} alkylphenyl, wherein the phenyl-group can be substituted with a group OH, NO_2, NH_2, CN, CH_3, Cl, Br;

R_5, R_6, R_7, which may be the same or different from one another, represent a hydrogen or C_{1-3} alkyl group; with the proviso that when R_1 or R_2 are benzyl or 4-hydroxybenzyl then R_3 and R_4 are isopropyl and an acceptable salt or enantiomer thereof.

2. (Amended) Compound[s] according to Claim 1, in which:

f, g, h, m, which may be the same or different from one another, may be 0 or 1;

R_1 and R_2 which may be the same or different from one another, represent the side chain of a natural amino acid selected from the group consisting of tryptophan, phenylalanine, tyrosine and histidine, or the side chain of a non-natural amino acid selected from the group consisting of:

tryptophan and phenyl alanine, either mono- or di-substituted with residues selected from the group consisting of C_{1-3} alkyl or halo-alkyl, C_{1-3} alkoxyl or amino-alkoxyl, halogen, OH, NH_2 and $NR_{13}R_{14}$, where R_{13} and R_{14}, which may be the same or different from one another, represent a hydrogen or C_{1-3} alkyl group;

R_3 is selected from the group consisting of:

– linear or branched alkyl having the formula C_nH_{2n+1} with n = 1-5 (selected from the group consisting of methyl, ethyl, propyl, isopropyl, n-butyl and t-butyl) cycloalkyl or alkylcycloalkyl of formula C_nH_{2n-1} with n = 5-9 (selected from the group consisting of: cyclopentyl, cyclohexyl and methylcyclohexyl)

$-(CH_2)_r$-Ar_1, where r = 1 or 2 and where Ar_1 is an aromatic group selected from the group consisting of: α-naphthyl, β-naphthyl, phenyl, indole, said Ar_1 group being possibly substituted with a maximum of two residues selected from the group consisting of: C_{1-3} alkyl, CF_3, C_{1-3} alkoxyl, Cl, F, OH and NH_2;

R_4 represents an L-Q group where:

L is a chemical bond of CH_2, and

Q is selected from the group consisting of:

– OH, NH_2, NR_9R_{10}, OR_{11}, and where R_9 and R_{10}, which may be the same or different from one another, represent a hydrogen or C_{1-3} alkyl group, C_{1-3}hydroxy alkyl, C_{1-3}dihydroxyaklyl, C_{1-3}alkyl-$CONHR_{12}$ (wherein R_{12} is a monoglycosidic group derived from D or L pentoses or hexoses (selected from the group consisting of ribose, arabinose. glucose, galactose, fructose, glucosamine and galactosamine and their N-acetylated derivatives)), C_{1-3}alkyltetrazole, C_{1-3}alkyl-COOH or wherein R_9R_{10} are joined together to form with the N atom a morpholine or a piperidine ring and where R_{11} is a C_{1-3} alkyl chain, or a C_{2-4} amino-alkyl chain;

– $NHCOR_8$ wherein R_8 is a cyclohexane containing from 2 to 4 OH groups, a C_{1-6} alkylchain containing a polar group (chosen in the group consisting of NH_2, COOH, $CONHR_{12}$, (wherein R_{12} is as hereabove defined) or [1,4']bipiperidine)

– COOH, $COOR_{17}$ or $CONHR_{12}$, wherein R_{12} is as hereabove defined and R_{17} is as R_{12} or a group 4-nitrobenzyl.

– R_5, R_6, R_7 are H[[] ,

in which the carbon atom that carries the substituents R_3 and R_7 has configuration R.

3. (amended twice) A compound according to Claim 2 selected from:

(a) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(b) Cyclo{-Suc-Trp-Phe-[(S)-NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(c) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_{11}$)-CH_2-NH]}

(d) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_4$(4-OCH_3))-CH_2-NH]}

(e) Cyclo{-Suc-Trp(5F)-Phe-[(R)- NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(f) Cyclo{-Suc-Trp(Me)-Phe-[(R)- NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(g) Cyclo{-Suc-Phe(3,4-Cl)-Phe-[(R)- NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(h) Cyclo{-Suc-Trp-Phe(3,4-Cl)- [(R)- NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(i) Cyclo{-Suc-Trp-Tyr-[(R)-NH-CH($CH_2C_6H_5$)-CH_2-NH]}

(j) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_3$-3,4-diCl)-CH_2-NH]}

(k) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH($CH_2C_6H_4$-4-OH)-CH_2-NH]}

(l) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-CH_2-C_6H_5)-CH_2-NH]}

(m) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-2-napthyl)-CH_2-NH]}

(n) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-indol-3-yl)-CH_2-NH]}

(o) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-5-F-indol-3-yl)-CH_2-NH]}

(p) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_4-3-F)-CH_2-NH]}

(q) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_3-3,4-diF-CH_2-NH]-}

(r) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_4-4-CF_3-CH_2-NH]-}

(s) Cyclo{-Suc-Trp-Phe-[(R)-NH-CH_2-CH($CH_2C_6H_5$)-NH]}

(t) Cyclo{-Suc-Trp-Phe-[(S)-NH- CH_2-CH($CH_2C_6H_5$)-NH]}

(u) Cyclo{-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-$(CH_2)_3CO$-}

(v) Cyclo{-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-N(CH_3)]-$(CH_2)_3CO$-}

(w) Cyclo{-Suc[1(S)-NH_2]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(x) Cyclo{-Suc[1(R)-NH_2]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(y) Cyclo{-Suc[2(S)-NH_2]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(z) Cyclo{-Suc[2(R)-NH_2]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(aa) Cyclo{-Suc[1(S)-NH(CH_3)]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(ab) Cyclo{-Suc[1-COO(CH_2-C_6H_4-4-NO_2)]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(ac) Cyclo{-Suc(1-COOH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]}
[Cyclo{-Suc(1-COOH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]}]

(ad) Cyclo{-Suc(1-OH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]}

(ae) Cyclo{-Suc(2-COOH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]}

(af) Cyclo{-Suc(2-OH)-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]}

(ag) Cyclo{-Suc[1(S)-(2H-tetrazolyl-5-ylmethyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}[.TFA] trifluoro-acetic acid

(ah) Cyclo{-Suc[1(S)-(morpholin-4-yl)]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}[.TFA] trifluoroacetic acid

(ai) Cyclo{-Suc[1(S)-N(CH_3)$_2$]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}[.TFA] trifluoroacetic acid

(aj) Cyclo{-Suc[1(S)-(piperidin-4-yl]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}[.TFA] trifluoroacetic acid

(ak) Cyclo{-Suc[1(S)-(N(CH_2CH_2OH)$_2$)]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]}[.TFA] trifluoroacetic acid

(al) Cyclo{-Suc[1(S)-(N($CH_2CH(OH)CH_2OH$)]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}[.TFA] trifluoroacetic acid

(am) Cyclo{-Suc[1(S)-(3-carboxypropanoyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}.

(an) Cyclo{-Suc[1(S)-[3-N'-ß-D-glucopiranos-1-yl)-carboxamidopropanoyl]amino]-Trp-Phe-[(R)NH-CH(CH_2-C_6H_5)-CH_2NH]-}

(ao) Cyclo{-Suc[1(S)-[(carboxymethyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}[. TFA] trifluoroacetic acid

(ap) Cyclo{-Suc[1(S)-[N'-ß-D-glucopiranos-1-yl)-carboxyamideomethyl]amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-} [TFA] trifluoroacetic acid

(aq) Cyclo{-Suc[1(S)-(chinyl)amine]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}

(ar) Cyclo{-Suc[1(S)-(4-aminobutanoyl)amino]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2- NH]-} [TFA] trifluoroacetic acid

(as) Cyclo{-Suc[1(S)-[1,4')bipiperidin-1-yl]acetamido]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}[TFA] trifluoroacetic acid

(at) Cyclo{-Suc[1-N-(ß-D-glucopiranos-1-yl)-carboxyamido]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}

(au) Cyclo{-Suc[1(S)-[N'-(2-N-acetyl-ß-D-glucopiranos-1-yl)-carboxyamido]-Trp-Phe-[(R)-NH-CH(CH_2-C_6H_5)-CH_2-NH]-}.

5. (Amended) A composition comprising a compound of general formula (I) according to Claim 1 in combination with a suitable carrier or excipient[s].

6. (Amended) A composition according to Claim 5, adapted for use as a tachykinin antagonist[s].

7. (Amended) A composition according to Claim 6, adapted for use as an antagonist[s] of the human neurokinin-2 (herein NK-2) receptor.

8. (Amended) A composition according to Claim 7, adapted for use in the treatment of the bronchospastic and inflammatory component of asthma, coughing , pulmonary

irritation, intestinal spasms, spasms of the biliary tract, local spasms of the bladder and of the ureter during cystitis, and kidney infections and colics.

12. (Amended) A method of antagonizing an NK-2 receptor in a mammal afflicted with asthma comprising contacting an NK-2 receptor in said mammal with a compound according to Claim 1 for a time and under conditions effective to antagonize an NK-2

13. (Amended) A method of antagonizing an NK-2 receptor in a mammal afflicted with an anxiety disorder comprising contacting an NK-2 receptor with a compound according to Claim 1 for a time and under conditions effective to antagonize an NK-2 receptor.

14. (Amended) A [M]method for the treatment of the bronchospastic and inflammatory component of asthma, coughing, pulmonary irritation, intestinal spasms, spasms of the biliary tract, local spasms of the bladder and if the ureter during cystitis, and kidney infections and colics, in which quantities of between 0.02 and 10 mg/kg of body weight of active principle consisting [of products] of formula (I), according to Claim 1, are administered to the patient for a time and under conditions effective to antagonize an NK-2 receptor.

16. (New) A method of antagonizing a neurokinin-2 (NK-2) receptor comprising contacting an NK-2 receptor with a compound according to claim 1 for a time and under conditions effective to antagonize said NK-2 receptor.

17. (New) A method of antagonizing a neurokinin-2 (NK-2) receptor comprising administering to a mammal in need thereof a compound according to claim 1 for a time and under conditions effective to antagonize the NK-2 receptor.

18. (New) The method according to claim 17 wherein said mammal is afflicted with a disorder selected from the group consisting of the bronchospastic and inflammatory component of asthma, coughing, pulmonary irritation, intestinal spasms, spasms of the

biliary tract, local spasms of the bladder and of the ureter during cystitis, and kidney infections and colics.